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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,851	09/09/1999	EDWARD M SELLERS	064658.0129	8120

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EXAMINER

DELACROIX MUIRHEI, CYBILLE

ART UNIT PAPER NUMBER

1614

DATE MAILED: 11/19/2003

15

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application N .

09/214,851

Applicant(s)

SELLERS ET AL.

Examiner

Cybille Delacroix-Muirheid

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 July 2003 and 09 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2,17-30,38-41,45 and 46 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2,17,18,21,22,25-30,38-41 and 45 is/are rejected.
- 7) ☒ Claim(s) 19,20,23,24 and 46 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

Detailed Action

1. Claim 38 is rejected under 35 U.S.C. 103(a) as being unpatentable over Garnitskij, supra in view of Modi et al., 5,653,987.
2. Claims 25-29, 38, 39, 40, 41 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

The following is responsive to Applicant's letter received Jul. 25, 2003 and the amendment received Sep. 9, 2003.

Claims 5, 6, 10-16, 31-33, 37, 42-44 are cancelled without prejudice or disclaimer. New claims 45-46 are added. Claims 2, 17-30, 38-41, 45 and 46 are currently pending.

The previous rejection of claims 11, 12, 13, 16 under 35 USC 103(a) over Garnitskij et al., maintained in the office action mailed July 17, 2003 is **withdrawn** in view of Applicant's amendment and the remarks contained therein.

The previous objection of claims 21 and 43 set forth at page 4 of the office action mailed July 17, 2003 is withdrawn in view of Applicant's amendment and the remarks contained therein.

The previous rejection of claims 11, 12, 13, 16 under 35 USC 112, paragraph 1, set forth at page 5 of the office action mailed July 17, 2003 is withdrawn in view of Applicant's amendment.

The previous rejection of claims 42, 44 under 35 USC 102(b) set forth at page 6 of the office action mailed July 17, 2003 is withdrawn in view of Applicant's amendment and the remarks contained therein.

The previous rejection of claim 43 under 35 USC 103(a) set forth at page 7 of the office action mailed July 17, 2003 is withdrawn in view of Applicant's amendment and the remarks contained therein.

Since, Applicant has not specifically traversed the rejection of claim 38 under 35 USC 103(a) maintained in the office action mailed July 17, 2003, the Examiner maintains this rejection for reasons which are already of record in the office actions mailed July 17, 2003 and Sep. 9, 2002.

Applicant's arguments traversing the previous rejection of claims 25-29, 38, 39, 40, 41 under 35 U.S.C. 112, first paragraph have been considered but are not found to be persuasive. Said rejection is maintained essentially for the reasons given previously in the office action mailed July 17, 2003 with the additional comments submitted below.

Finally, Applicant's letter received July 25, 2003 has been considered and noted. A written translation of the Russian document is in the process of being obtained.

Concerning Applicant's arguments traversing the previous claim rejection under 35 USC 112, paragraph 1, it is essentially Applicant's position that the application as filed provides a clear description of the various disorders other than nicotine-related

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disorders which require the regulation of nicotine metabolism to cotinine. Applicant directs the Examiner attention to page 18, lines 25-31 of the specification.

Applicant's arguments have been considered but are not found to be persuasive.

The Examiner respectfully submits that there is insufficient descriptive support for the generic limitation "a condition requiring regulation of nicotine metabolism to cotinine." The reference at page 18, lines 25-31 of the specification does not provide sufficient descriptive support for such a limitation. There is no clear description indicating that conditions, other than nicotine use disorders, were known to Applicant. In fact, the Examiner respectfully submits that the language upon which Applicant relies implies the treatment of conditions separate and distinct from nicotine use disorders.

Specifically, the phrase

"the methods and compositions of the invention in treating individuals with nicotine use disorders and nicotine-induced disorders **are also** useful in the treatment and prophylaxis of diseases or conditions, including nicotine-related disorders such as opioid related disorders, proliferative diseases Examples of such underlying diseases or conditions include malignant disease, psychosis, schizophrenia, Parkinson's disease", etc. (please see page 18, lines 25-31)

In other words, this description appears to address another embodiment of the invention, i.e. the treatment of other disorders such as psychosis. The Examiner respectfully submits that the description at page 18, lines 25-31 does not provide one of ordinary skill in the art with some understanding of the conditions to be treated by the claims, and one of ordinary skill in the art would not have concluded that Applicant was in possession of the method as claimed.

It is for these reasons that the rejection is maintained.

New Ground(s) of Rejection

Upon reconsideration of the claims with a Primary Examiner, the Examiner respectfully submits the following new ground of rejection.

The allowability of claims 17-20 and 22-23 is withdrawn in view of the following new ground(s) of rejection.

New Ground(s) of Rejection

Claim Objections

3. Claims 29, 45 are objected due to the following informalities: a substance cannot comprise a "plurality of compounds". In claim 45, line 3, the term —or—should be added after "neurological". Appropriate correction is required.

Claim Rejections—35 USC 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 41 and 45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 41 recites the limitation that "at least one of said substances is methoxsalen or a derivative." However, such a limitation renders the claim vague and indefinite because it is not clear to which substance (in claim 38) Applicant is referring. The Examiner respectfully suggests amending line 1 of claim 41, to read —said first substance is methoxsalen or a derivative thereof--.

6. Claim 45 requires the treatment of "conditions requiring regulation of nicotine metabolism to cotinine, wherein the condition may be mental disorders, proliferative diseases, Parkinson's disease, depression, anxiety, etc. Please see claim 29. When analyzed in view of Applicant's specification, the Examiner respectfully submits that the claim is not adequately described and is therefore vague and indefinite.

At page 18, lines 25-31, the specification describes

"the methods and compositions of the invention in treating individuals with nicotine use disorders and nicotine-induced disorders **are also** useful in the treatment and prophylaxis of diseases or conditions, including nicotine-related disorders such as opioid related disorders, proliferative diseases Examples of such underlying diseases or conditions include malignant disease, psychosis, schizophrenia, Parkinson's disease", etc. (please see page 18, lines 25-31)

This description does not appear to establish a correlation between nicotine use and the claimed disorders. Instead, it appears to describe another embodiment of the invention, i.e. the treatment of other disorders, which are separate and distinct from nicotine use disorders. Furthermore, the Examiner is unaware of any reference or text, which establishes a link between nicotine use and depression, Parkinson's disease, schizophrenia, proliferative diseases etc.

Moreover, the terms "proliferative disease", "malignant disease", "opioid related disorders", "cognitive, neurological or mental disorders" and "other drug dependencies" are generic terms/descriptions. Yet, the few specific diseases listed as examples in the specification (page 18, lines 25-31) are only illustrative and do not adequately define what applicant intends to be within the scope of the invention.

As a result, one of ordinary skill in the art would not be readily apprised of the scope of the invention, and the metes and bounds of the patent protection desired are unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17, 2, 18, 21, 22, 25, 26, 29, 30, 38 and 45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for coumarin, orphenadrine, 7-methylcoumarin, 7-methoxycoumarin, 7-ethoxycoumarin, naringenin, methoxsalen and diethyldithiocarbamic acid, does not reasonably provide enablement for all substances which selectively inhibit CYP2A6 and substances which inhibit CYP2B6 and effectively enhance inhibition of nicotine metabolism or regulate the metabolism of nicotine to cotinine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples;

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and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to a method of enhancing inhibition of nicotine metabolism and a method of treating a condition requiring the regulation of nicotine metabolism to cotinine by administering effective amounts of a substance which selectively inhibits CYP2A6 and an inhibitor of CYP2B6. There is also a claim to a pharmaceutical composition for regulating the metabolism of nicotine to cotinine comprising effective amounts of a substance, which selectively inhibits CYP2A6 in combination with an inhibitor of CYP2B6. Dependent claim 45 requires the treatment of specific diseases such as Parkinson's disease, other drug disorders, malignant disease, schizophrenia, etc.

(2) The state of the prior art

The art recognizes the addictive effects of nicotine, particularly in smokers, and the numerous therapeutic approaches aimed at nicotine replacement therapy, i.e. nicotine patches, nicotine chewing gum, etc.

(3) The relative skill of those in the art

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and chemical art is high.

(5) The breadth of the claims

The claims are very broad and encompass the treatment of numerous disorders using any substance, which would bind to a CYP2A6 and CYP2B6.

(6) The amount of direction or guidance presented

Applicant's specification provides guidance for and is only enabled for the use of coumarin, orphenadrine, 7-methylcoumarin, 7-methoxycoumarin, 7-ethoxycoumarin, naringenin, methoxsalen and diethyldithiocarbamic acid in the regulation of nicotine metabolism thereby treating dependent smokers. However, the specification provides no guidance to enable one of ordinary skill in the art to use the invention commensurate in scope with the claims, which, as stated above, are broad and encompass the use of numerous compounds for the treatment of a broad range of disorders. In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940), gives this general rule: "It is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result." Applicant's specification does not set forth a representative number of examples of compounds, which would bind to CYP2A6 and CYP2B6, enhance inhibition of nicotine metabolism or regulate nicotine metabolism to cotinine and ultimately treat the claimed disorders.

With respect to claim 45, there is no guidance to enable one of ordinary skill in the art to use CYP2A6 and CYP2B6 inhibitors or even the use of coumarin, orphenadrine, 7-methylcoumarin, 7-methoxycoumarin, 7-ethoxycoumarin, naringenin,

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methoxsalen and diethyldithiocarbamic acid in the treatment of Parkinson's disease, malignant disease, proliferative diseases, schizophrenia, psychosis, anxiety, depression, alcoholism, opiate dependence, other drug dependencies, opioid related disorders and cognitive, neurological or mental disorders.

(7) The presence or absence of working examples

The examples in Applicant's specification provide working examples, in vitro as well as clinical, demonstrating the use of coumarin, orphenadrine, 7-methylcoumarin, 7-methoxycoumarin, 7-ethoxycoumarin, naringenin, methoxsalen and diethyldithiocarbamic acid for inhibiting nicotine metabolism. There are no working examples demonstrating the use of such compounds in the treatment of Parkinson's disease, malignant disease, proliferative diseases, schizophrenia, psychosis, anxiety, depression, alcoholism, opiate dependence, other drug dependencies, opioid related disorders and cognitive, neurological or mental disorders.

Therefore, the specification enables one of ordinary skill in the art to use the compounds mentioned above in the method and composition for enhancing the inhibition of nicotine metabolism, i.e. regulating the metabolism of nicotine to cotinine, for use in the treatment of dependent smokers.

(8) The quantity of experimentation necessary

Since (1) the unpredictability of the chemical and pharmaceutical art is high, (2) chemical compounds differ radically in their properties, (3) Applicant's specification does not provide a representative number of compounds which would be capable of accomplishing the claimed methods and composition, (4) the only working examples in

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the specification are directed to the use of a limited number of compounds for inhibiting nicotine metabolism thereby treating dependent smokers, and (5) since compound structure and activity for pharmaceutical use must be determined from case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue experimentation to determine all compounds which would selectively inhibit CYP2A6 and CYP2B6 and which, in pharmaceutical form, would be capable of accomplishing the claimed methods.

8. Claims 19, 20, 23, 24, 46 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 2, 17, 18, 21, 22, 25, 26, 27, 28, 29, 30, 38, 39, 40, 41 and 45 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cybille Delacroix-Muirheid whose telephone number is 703-306-3227. The examiner can normally be reached on Mon-Fri. from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marianne Seidel, can be reached on (703) 308-4725. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.


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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

CDM



Nov. 16, 2003



RAYMOND HENLEY, III
PRIMARY EXAMINER
GROUP 1000